Monitoring of biochemical markers of septic states.

PhD Thesis was elaborated within Postgraduate Studies in Biomedicine at the Institute of Clinical Chemistry and Laboratory medicine of the First Faculty of Medicine, Charles University in Prague, and was supported by research preject No J13/98:111100002-1

Author: MUDr Helena Brodská

Address : Institut of Clinical Biochemistry and Laboratory Diagnostic of the 1.st Faculty of Medicine and General University Hospital.
U Nemocnice 2, 128-08, Prague 2
Tel: 224962897, Fax 224962840
e-mail brodska@vfn.cz

Commission : Biochemistry and Pathobiochemistry

Supervisor : Prof MUDr Antonín Kazda DrSc

Oponents : Prof MUDr Richard Průša CSc, Doc MUDr Roman Zazula PhD

PhD Thesis Report sent :

Defence of PhD Thesis :

Place of Defence

Chairman of the Commission Biochemistry and Pathobiochemistry :

Prof MUDr Jiří Kraml DrSc

CONTENS

2. SOUHRN

Problematika systémového zánětu, (systemic inflammatory response syndrome-SIRS), resp.sepse je v poslední době velice diskutovaná a to napříč medicínskými obory. Včasná diagnóza a následně adekvátní terapie snižuje rizika jejich rozvoje. Je tedy obecně snahou najít vhodný marker pro diagnostiku a monitoraci průběhu. Každým rokem se objevují nové markery, které mozajkovitě doplňují patofyziologický obraz, ale marker, který by splňoval podmínky specifity, senzitivity, dostupnosti, stále nemáme. V posledních 10 letech je za jeden z nejnadějnějších považován prokalcitonin (PCT).

V rámci sledování zánětlivých parametrů, resp. jejich chování ve stavech systémového zánětu jsem se soustředila hlavně na prokalcitonin a jeho jakoby nesouhlasné nálezy s přítomností infektu a s ostatními parametry zánětu. A to nejprve ve studii porovnávání sensitivity a specifity PCT a dalších vybraných zánětlivých parametrů v klinicky definovyných stavech, kde potvrzuje PCT svoje vyjímečné postavení.V dalších studiích jsem se zaměřila na elevace PCT při nepřítomnosti akutního infektu. A to nejprve ve studii s pacienty v transplataci kostní dřeně, kde významné elevace souvisí spíše s rozpadem leukocytů a hepatotoxicitou způsobenou podáním ATG. Ve studiích s pacienty v konečné fázi renálního selhání se neinfekční elevace jeví spíše jako projev tíže stavu. V závěrečné studii jsme potvrdili vztah PCT k tíži stavu a ke stavu antioxidační ochrany, respective plasmatické hladině selenu. Ve zmíněných studiích bych ráda prezentovala dignostickou šíři tohoto, asi v současné době nejpoužívanějšího markeru systémového zánětu. Chtěla bych zdůraznit důležitost správné indikace, interpretace v souvislosti s dalšími parametry a hlavně s klinickým stavem. PCT představuje při téměř 10 letech užívání v klinické praxi stále dobrý biologický diagnostický marker sepse nebo septického šoku. Jeho výpovědní hodnota je zde nadřazená C-reaktivnímu proteinu (CRP) a dalším proteinům akutní fáze. Popisuje tíži stavu, rozsah systémové odpovědi, jednoznačně diagnostikuje přítomnost systémové bakteriální infekce. Měl by být součástí diagnostických postupů

(guidelines) pro sepsi, stává se vodítkem v zahájení a ukončení antibiotické terapie a součástí klinické praxe na JIP. Hodnoty PCT přispívají k identifikaci nemocných s nepříznivou prognózou přežití těžkých bakeriálních infekcí-sepsí.

3. SUMMARY

The topic of systemic inflammatory response is lately often discussed across the whole field of medicine. Early diagnosis and the following adequate therapy minimize the risks of the development of systemic inflammatory response syndrome (SIRS). Therefore there is a general urge to find an appropriate marker for diagnosing and monitoring of the development of SIRS. Each year new markers appear, markers that fill up the mosaic of a pathophysiological picture, but we still do not have a marker, that would fulfill the demands of specificity, sensitivity and availability. In the recent ten years, one of the most promising markers seems to be the PCT.

Within the frame of monitoring the inflammatory parameters, or rather their behavior in the SIRS, I have focused mainly on procalcitonin and its seemingly divertive results in connection with the appearance of infection and with other parameters of the inflammation.

In the first study, I have focused on comparing the sensitivity and specificity of the PCT and other inflammatory markers in defined clinical states (SIRS, MODS). PCT proved its best prognostic and diagnostic value. In other studies I focused on elevations of PCT in patients without acute infect. This is discused in a study with patients undergoing blood stem cells transplantation, where the elevations of PCT are rather due to the destruction of white blood cells (WBC) and hepatotoxicity, caused as a reaction to ATG administration.

In two studies with patients in end states renal diseases (ESRD) the non infectious elevations appear as marker of severity of clinical state. In the last study we confirm the relationship between PCT and severity of clinical state and the antioxidative defence, respectively the plasmatic selenium level. In the above mentioned studies I would like to present the wide range of this marker, which in the meantime is one of

the most used markers of the SIRS. I would like to stress the importance of a correct indication and of an accurate interpretation in accordance with all the other parameters, but most of all with the clinical state. PCT, being almost ten years in use in clinical praxis, still represents a good biological diagnostic marker of sepsis or septic shock. Its informative value is higher than CRP and other proteins of the acute phase. It describes the condition of a patient and the range of reactions of the system. It diagnoses accurately the presence of bacterial infection in the system. It should be a part of diagnostic guidelines for sepsis, it guides the beginning and the end of an antibiotic therapy, and it should be part of a clinical praxis at JIP as well. The PCT values contribute to identification of patients with critical prognosis to survive hard bacterial infections/sepsis.

4. INTRODUCTION

Infection is primarly a defense of the organism. It helps the organism, in the whole range of its appearances, both on local and systemic level to deal with the critical noxis, infectious (bacterias, viruses, mycosis) as wall as noninfectious (physical, chemical destruction) origin. On more levels and in more systems, all interconnected, a search for identification, localization, destruction of agens is going on. At the same time, the establishment of recovering mechanisms is going on recovering the function on both the local and the systemic inflammation.

Today, a proven function of the first contact have the Toll like receptors, that react to specific matrices. These are included in groups of pathogens and through activation of nuclear factor kappa B (NF-kapaB) initiates the transcription of proximal cytokins (Interleukin IL- lbeta, IL- 6, TNF alfa.). These activates other systems, as the monocyto-macrofag system, complement, coagulation cascade, blood plateles, derivates of arachidonic acid (tromboxan, prostaglandin), that cause changes in the reactivity of the venous wall. They also activate adhesive molecules, acute phase proteins, and last but not least the stress hormones.

At the same time a large amount of oxygen radicals appears. They attack the endothel and accelerate the changes. The impact of oxygen radicals is generally believed to be decisive in pathogenesis of systemic inflammatory response. The above mentioned reaction is

uniform, and is provoked by any kind noxis (both infectious and noninfectious). The range of systemic inflammatory response can influence the gene polymorphism of the main pro- and anti- inflammatory cytokines, especially TNF-alfa, IL-1beta, IL-6, IL-8 a IL-10.

Among other influencing factors are: the type of infection agens, the quality and intensity of hormonal response, the intensity of oxidative stress, and the capacity of the organism to respond to it. For an early diagnosis and monitoring of the development of the inflammation, we can monitor a palette of inflammatory markers, markers of metabolic response and markers of oxidative stress.

Monitoring of these markers and evaluation of their diagnostic value – not only in septic condition – is the topic of this paper.

5. AIMS

5.1. MONITORING OF SELECTED INFLAMMATORY MARKERS. EVALUATION OF THE SPECIFITY AND SENZITIVITY OF THESE MARKERS IN DEFINED CLINICAL STATES.

.

5. 2. DETERMINATE THE DIAGNOSTIC AND PROGNOSTIC VALUE OF PCT IN PATIENTS UNDERGOING STEM CELLS TRANSPLANTATION.

5.3. DETERMINATE THE DIAGNOSTIC AND PROGNOSTIC VALUE OF PCT IN ESRD PATIENTS .

Correlations with PCT and other inflammatory markers and with markers of bone metabolism.

.

5.4. PCT AND OXIDATIVE STRESS, RELATIONSHIP TO SELECTED MARKERS OF ANTIOXIDATIVE DEFENSE.

Correlation between PCT, severity of clinical state and selenium plasmatic levels.

6. MATERIALS AND METHODS

6.1. STUDIED GROUPS

6.1. 1. The aim of fist study was to evaluate diagnostic specificity and sensitivity of procalcitonin (PCT), to compare PCT to C-reactive protein (CRP) and other markers of acute phase reactants in relation to clinical status and microbiological examinations. A prospective study in ICU patients. One hundred and sixty-four examinations of PCT, CRP, orosomucoid, prealbumin, fibrinogen, INR, leukocyte and platelet count were evaluated in 43 patients. The APACHE II score was calculated on admission, the SOFA daily. SIRS, MODS, positivity of bacteriological, hemoculture and apparent infection were also assessed.

6.1.2.In the second study we prospectively evaluated a cohort of twenty-six adult patients indicated for ATG conditioning regimen prior to haematopoietic stem cell transplantation in an observational non-randomized study. The patients without clinical signs of infection were prospectively studied. ATG was administered in up to three doses over 5 days. PCT, CRP, white blood count (WBC), urea, creatinine, glomerular filtration rate (GFR), bilirubin, alanin amino-transferase (ALT) and gamma-glutamyl transferase (GGT) were assessed daily during ATG administration. Pharyngeal, nose and rectal swabs and urine samples were cultured twice weekly. Blood cultures were obtained if clinical symptoms of infection were present.

6.1.3.1. In the next two studies with ESRD patiens there were blood samples from 54 HD patients obtained prior and after the HD, 42 healthy blood donors were examined

as controls. Blood levels of calprotectin, procalcitonin, C-reactive protein and intracellular production of IL-10 and IL- 12 in monocytes were determined in both groups.

6.1.3.2.In the study, where we evaluated the interrelationship of PCT to other markers of calcium and/or bone metabolism we determined IL-10 intracellular production in monocytes, PCT, plasmatic calcium – Ca, plasmatic phosphorus – P, alkaline phosphatase - ALP, parathormone - PTH, calcitonin – CAL, cross-linked carboxyterminal telopeptid of type I collagen – ICTP.

Dialysis was carried out with the Dialog + (BBraun), AK 200 Ultra S (Gambro) and Fresenius 4008 S (Fresenius), the dialysators were from synthetic (Polyflux L, Diacap) or diacetate (Dicea), triacetate (Tricea) membranes. Blood samples were obtained just prior to the start of dialysis (T_0), and immediately after the termination of HD (T_1) and were drawn from the fistula or the permcath.

6.1.4. In the last study we evaluated the influence of high doses of selenium on selected clinical and laboratory parameters in critically ill patients. 140 patients (78 m, 62 f,) were randomized into groups A and B. Group A received standard Se substitution: 30-75 μg of NaSelenite i.v./day. Group B received high dose Se substitution according to a protocol: 1000 μg at day 1, following with 500 μg at days 2-14 of NaSelenite i.v. These groups we devided into 4 subgroups: SIRS, sepsis, severe sepsis and septic shock. Plasma levels of Se, CRP, PCT, were examined each other day. SOFA and 28-day mortality were evaluated as clinical markers. Relations between observed parameters were evaluated statistically. In both groups transitions among subgroups during treatment were evaluated. All patients monitored less than 3 times were excluded.

6.2. LABORATORY EXAMINATION

All rutine biochemical parameters as urea, kreatinin, albumin, prealbumin, orosomucoid, CRP, cholesterol, Ca, P, ALP, AST, ALT, GGT, beta 2- mikroglobulin

were determined with standard clinical-chemistry methods recommended by the International Federation of Clinical Chemistry (IFCC). IL10 intracellular production in monocytes (flow cytometry, FACS Canto, BD), Plasmatic calprotectin and serum PCT were measured by enzyme-linked immunosorbent assays (MRP8/14 Bűhlmann and Vidas Brahms, respectively) PTH (ECLIA), calcitonin – CAL (IRMA), cross-linked carboxyterminal telopeptid of type I collagen – ICTP (RIA).Selenium by atomic absorption spectrometry with electrothermic atomisation (AAS), GSHPx with UV method (RANDOX). WBC was analyzed from K_3 EDTA samples by a blood count analyser (Advia 120, Bayer).

6.3. STATISTICAL ANALYSIS

Distributions of laboratory test results are described as mean ± SD or interquartile range for quantitative items as stated. Correlation between levels of markers were examined with Spearman's rank correlation coefficient. To assess the accuracy of markers in groups of patients compared to controls, the Mann-Whitney *U* test was performed using the Statistica CZ program, version 7.0 (StatSoft Inc., OK, USA). *p* value smaller than 0.05 was considered significant.

7. RESULTS

7.1. PCT was a more effective marker of sepsis-related complications in ICU patients than CRP or other acute phase reactants. ROC analysis was a suitable tool for confirmation of these relations.

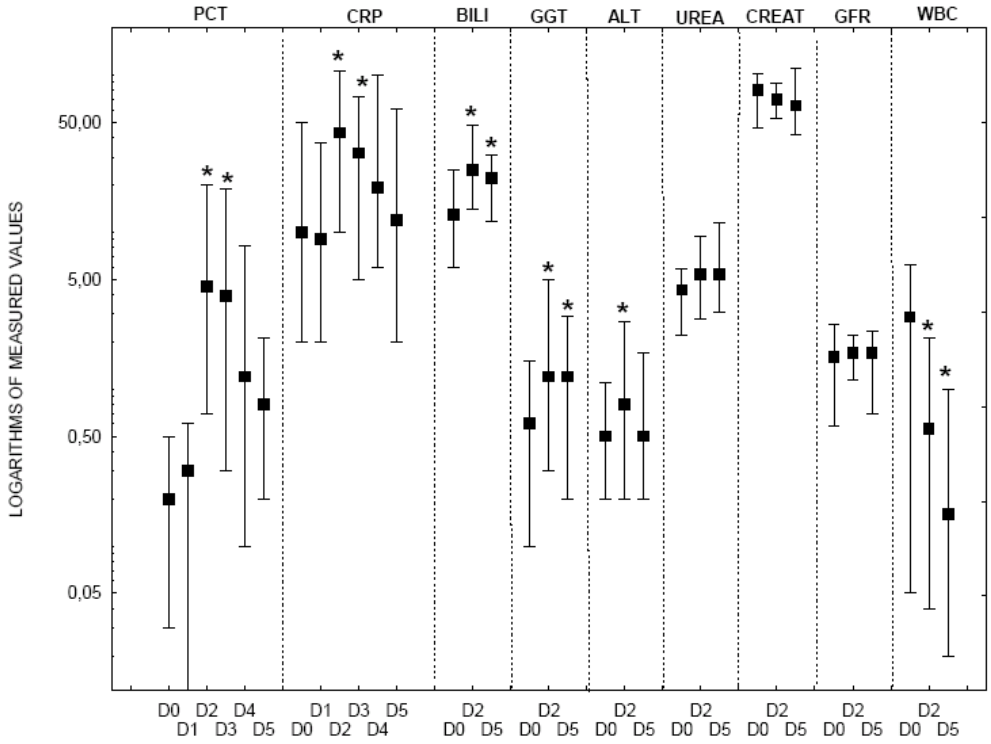
Table 1. AUC is given for the following variables.

	CRP	**leukocyty**	**orosomukoid**	**PCT**
APACHE	**0,580**	**0,596**	**0,571**	**0,605**
hemoculture	**0,545**	**0,475**	**0,663**	**0,520**
Bacteriological finding	**0,492**	**0,539**	**0,575**	**0,627**
MODS	**0,490**	**0,569**	**0,540**	**0,683**
SIRS	**0,564**	**-**	**0,512**	**0,694**
SOFA	**0,557**	**0,657**	**0,523**	**0,756**
marked infect	**0,528**	**0,588**	**0,476**	**0,598**
survival	**0,546**	**0,610**	**0,472**	**0,716**

7.2. A significant increase in PCT was observed starting 24 h after ATG administration. The initial surge was followed by a slow, steady decrease. On Day 5, PCT levels were still increased, but there was no statistical difference vs.base levels (BL). The dynamics of CRP changes were similar to PCT, but CRP returned to BL values one day earlier. Similar statistically significant trends were observed for bilirubin and GGT. In contrast, ALT increased only transiently on day 2. There were no changes in urea, creatinine or GFR during conditioning. Progressive depletion of leukocytes was observed over time. There was no statistically significant

interrelationship PCT levels and markers of renal functions ($p < 0.05$ for all comparisons). Basal levels of PCT before ATG administration were (0.185/ 0.06/ 0.30), (1st, 2nd, 3rd quartile) and of CRP (10/ 5 /26). The second day after ATG administration, there was a routine PCT elevation, max.183, minim. 0.8 (5.0/ 1.6/ 26) and CRP max 107, min 10 (44/ 21/ 64). The first day leukocyte values max 10.9 x 10e9/l, min 0.06 (2.,88/ 1.55/ 4.32) compared to the second day values max 3.5 min 0.03 (0.56/ 0.1/ 1.22), which was statistically significant ($p = 0.005$).

Table 2. Dynamic of changes value of monitoring markers



7.3. 20% of all ESRD patients had elevation of PCT. None of CRP, calprotectin, IL-10, IL-12 correlated with plasma PCT, neither prior nor after HD. None of PCT, CRP, IL- 10 and IL- 12 correlated with calprotectin. Concentrations of plasma calprotectin in all ESRD patients were significantly higher than in healthy controls ($p<0.05$). No differences

between pre- and post-HD PCT, CRP calprotectin and IL 10and IL12 plasma levels were observed. Plasma PCT, CRP and calprotectin levels were not significantly influenced by the presence of diabetes. A significant positive correlation of plasma calprotectin to plasma beta-2 microglobulin was proven ($p < 0.05$). Elevation of plasma calprotectin correlated strongly to the hemodialysis vintage ($r=0.55$, $p<0.01$).

Interrelationship of PCT and other markers of calcium and bone metabolism presents table 3.

Table 3. PCT and markers of bone metabolism

(Spearman's rank correlation test) – prior HD* **p** < 0.05 ** **p** < 0.001

r	**Ca x P**	**Ca**	**P**	**PCT**	**CAL**	**PTH**	**IL-10**	**ICTP**	**ALP**
Ca x P	x	0.55 **	0.95 **	0.32 *	0.06	-0.03	0.04	0.1	-0.07
Ca	x	x	0.3 *	0.21	0.23 *	-0.13	0.004	0.02	-0.29
P	x	x	x	0.39 **	0.07	0.02	0.026	0.17	0.09
PCT	x	x	x	x	0.71 **	-0.07	-0.1	0.35*	0.22
CAL	x	x	x	x	x	-0.16	-0.12	0.22	0.07
PTH	x	x	x	x	x	x	0.11	0.14	0.04
IL-10	x	x	x	x	x	x	x	- 0.32 *	0.006
ICTP	x	x	x	x	x	x	x	x	0.28 *

7.4. Standard Se substitution- group A (30-75 µg/d) is not sufficient in critically ill for restoring and keeping the physiologic plasma levels of selenium.In our patients with high doses- group B, Se subtitution, 1000 ug 1st day, followed by 500 µg/d for two weeks normalized serum Se level and GSHPx level (without adverse reactions). There was statistically significant increase of cholesterol levels and decrease of SOFA in patients with high Se supplementation. There was no statistical improvement of 28-day mortality in our patients with high dose Se substitution.There were more significant negative correlations between plasmatic Se and parameters of inflammation in group of patients supplemented with high doses of selenium. This statement was in accordance with finding of more frequent transition from septic shock to less severe stage of sepsis. Even if decrease of mortality was not found, presented results may perhaps indicate positive metabolic influence of high Se supplementation in critical illness.

Table 4. Correlation between inflammatory markers and Selenium

Parameter	Group A	Group B	Significance
Se x PCT	r = -0.24	r = -0,42	p < 0,05
Se x CRP	r = -0,41	r = -0,53	p < 0,05
Se x SOFA	r = -0,29	r = - 0,03	N.S.

8. DISCUSION

In the first study, using the ROC analyze, we conclude AUC more than 0,6 was only body temperature (0,696), PCT (0,683) a blood plateles (0,658). AUC for CRP was only 0,490. PCT has a clear priority also regarding the diagnosis and differentiation of MODS severity. In accordance with a number of studies that compare a predictive or diagnostic PCT value with proteins of the acute phase, our results confirm the fact,

that the sensitivity and specificity of PCT in patients with bacterial inflammation is higher than in the case of CRP and other proteins of the acute phase.

In the second study we evaluated diagnostic and prognostic value of PCT in patients undergoing conditioning with ATG before stem transplantation. We observed a characteristic early surge in PCT and CRP, followed by a steady decline to a near-normalization on day 4. Yet, this was not associated with clinical infection, as monitored by microbiological cultures. Thus, neither PCT nor CRP proved useful as a valid complementary diagnostic tool at this setting.The exact function, mechanism and the site of PCT production is yet to be fully unveiled. In our study, induction of PCT increase by ATG administration can be explained mainly by lymphocytes destruction. However, the contribution of hepatotoxicity must also be considered. As the dynamics of PCT and CRP changes are similar, we do not believe that a difference in half-time of these parameters plays a role here. Understanding the mechanisms of PCT release could help to elucidate its increase in other non-infectious conditions, as described below. The extent of this increase in our cohort was not dependent on initial liver and renal functions or WBC. It was not predictive within the context of subsequent infectious complications and/or mortality. It could be speculated that the extent of PCT increase is related to a certain immunological body reserve that may not be fully reflected by actual WBC.

In the next two studies with the end state renal diseases (ESRD) patients we monitored again the elevations of PCT without present acute infection.We tried to explain it.The elevations of PCT we found in 20% of all patients. In the first of these studies we monitored correlations of PCT with the other inflammatory markers. It is known that inflammation is a major risk factor for mortality in patients with ESRD . Inflammation is a complex process that reflects the local and systemic responses to different immunological and non-immunological stimuli. Inflammation can be initiated by different ways and is characterized by activation of acute phase response and release of specific markers. The causes of ongoing inflammatory process in ESRD patients is not well understood, but it is accepted that continuous exposure to an inflammatory stimulus (e.g. uremia, oxidative stress and endotoxin exposure) results in local and systemic cell activation. In addition to these proinflammatory conditions, patients on hemodialysis are exposed to different external stimuli, such as high/low flux dialysis,

bioincompatible membranes, dialysate contamination, and access site infections. Polymorphonuclear leukocytes (PMNLs) play a crucial role in inflammatory cascade in ESRD patients. The main inflammatory mediator of PMNs is calprotectin. In our findings, plasma calprotectin is significantly higher in ESRD patients compared to healthy controls. Significantly elevated levels of plasma calprotectin in ESRD patients occur without an acute infectious cause and are not affected by the presence of diabetes. By analogy to plasma beta-2 microglobulin, close relation of plasma calprotectin to HD vintage was shown.Considering outstanding inflammatory properties of calprotectin, there seems to be a discrepancy between high concentrations of plasma calprotectin and lack of correlation with other systemic inflammatory markers such as PCT, CRP, IL-10 and IL-12, never prior nor after HD, suggesting that these inflammatory markers occur independently of each other. In the second study with ESRD patients we determined relation between PCT and markers of bone metabolism. Elevated plasmatic concentration of P and increased CaP product indicates the degree of renal damage. Thus, the strong positive correlation with PCT seems to be of prognostic significance and might be helpful to identify patients of poor prognosis because of the end-stage chronic renal disease but not because of the systemic infection. We have noticed a close correlation between PCT and ICTP. Nevertheless, plasmatic level of ICTP was elevated in all patients before HD and significantly decreased after HD ($p < 0.05$) , unlike PCT. We have noticed significant negative correlation of ICTP with intracellular production of IL-10 in monocytes. IL-10 is an important endogenous suppressor of infection-stimulated bone resorption in vivo, so that its decreased intracellular production in end-stage chronic renal disease probably contributes to the alteration of the bone metabolism in these patients. No correlation between Ca, PTH, ALP and IL-10 on one hand and PCT on other hand was found neither before, nor after HD, as well as no correlation with diuresis and presence of DM, or secondary hyperparathyreoidism.We noticed correlation with Ca x P and with ICTP and we conclude the PCT elevation probably presents severity of clinical states again.

In last study we monitored PCT and selected markers, witch may have the influence on oxidative stress. In group patients with high doses of selenium (Se) we noticed significant higher level of plasmatic Se and Gluthationperoxidases (GSHPx), higher

increase of plasmatic cholesterol and decrease of SOFA. Also we noticed negative correlation between PCT, CRP and Se plasmatic levels in patients in septic shock. Plasmatic level of Se decreases in patients with hard SIRS, or with septic shock on 50% value. The value under 0,7 umol/l represents 3 times higher risk of incidence of ventilator association pneumonia (VAP) and increase 4 times mortality. The last guidelines recomended i.v.Na-selenit, Na-selenit pentahydrát in doses 400ug Se/day Marked negative correlation between plasmatic Se levels and PCT, CRP confirms relationship between severity of clinical states, respectively development of SIRS, sepsis (high plasmatic levels of PCT, CRP) and selenium plasmatic levels.

9. CONCLUSIONS

1. In accordance with a number of studies that compare a predictive or diagnostic PCT value with proteins of acute phase, our results confirm the fact, that the sensitivity and specificity of PCT in patients with bacterial inflammation is higher than in the case of CRP and other proteins of the acute phase. PCT has a clear priority also regarding the diagnosis and differentiation of MODS mortality. PCT is not used for finding out a local bacterial infect, it does not replace the informative value of proteins of the acute phase, especially CPR at an early stage of recognizing the infection.

2. On the contrary, we often find PCT elevations that are not caused by infectious noxis in diagnosis of critically ill patients. However, this does not make PCT less important. On the contrary, it gives us another diagnostic dimension. PCT shows us the seriousness of the patient´s state, the range of reactions of the system, as we have mentioned them in the study on patients with transplantation of blood plates. PCT provides an accurate picture about an infection inflammation in neutrophenic patients, in cases, where the number of leucocytes, the body temperature and sometimes even CRP have no diagnostic value.

3. It is discussed, that PCT is in relation to the changes in bone metabolism in patients with ESRD. Because of the suggested correlation, the PCT elevation in these patients is indicating the seriousness of their condition and the range of damage. It is therefore

assumed, that it does not directly coincide with the metabolism of calcium. The presence of chronic inflammation in these patients is better described by calprotectin.

4. We have proven a clear correlation between Se value and PCT value in serious sepsis patients and patients in septic shock. In relation to increasing PCT value, the plasmatic value of Se decreases. If Se and GSHPx are the milestones of organisms defense against ROS, then PCT increased value server as an indicator of the severity of condition.

From the knowledge we have till now, we can draw following indication of PCT:

Monitoring of critically ill patients - long term high values have worse prognosis.

The control of the therapy and of the development of bacterial infection.The development of value level reflects increasing or decreasing immune reaction to infection, so the dynamics is important.

PCT and the changes of dynamics indicates the beginning and end of ATB therapy in defined clinical states.

Diferencial diagnostic of systemic bacterial infect and fever of unknown origin.

Diferencial diagnostic of systemic autoimmune disease and bacterial complication of these patients.

Prognostic effect of PCT level for patients with MODS or sepsis.

10. REFERENCES:

MORENO, RP., METNITZ, B., ADLER,R., et al. Sepsis mortality prediction based on predisposition, infection and resoponse. Intensive Care Med, 2008, 34, p. 496-504.

HOŘEJŠÍ V., BARTUŇKOVÁ J. Základy imunologie. Praha Triton 2002

HERNDON, DH, WERNERMAN, J. Brussels 200, Roundtable on metabolism in sepsis and multiple organ failure. J Paren Enter Nutrition, 2008, 32, 1, p. 1-5.

MÜLLER, B. Endocrine aspects of critical illness. Ann Endocrinology, 2007, 68, p. 290-298.

SUTHERLAND AM., WALEY KR. Association of genetic variation with sepsis.ritical Care 2009, 13:210

SOBOTKA, L., SOETERS, PB. Metabolic response to injury and sepsis. In Sobotka L. (Ed.) Basics in Clinical Nutrition. Praha: Galén, 2004, p. 124-129.

SATURNINO, S., ANDRADE, M. Toll-like receptors, new horizons in sepsis. Current Molecul Med, 2007, 7, p. 522-531.

MARUNA,P. Proteiny akutní fáze. Praha: Maxdorf, 2004, 282 s.

SHENKIN, A. The key role of micronutrients. Clin Nutr, 2006, 25, p. 1-13.
FORCEVILLE, X., VITOUX, D., GAUZIT,R. Selenium, systemic immune response syndrome, sepsis and outcome in critically ill patients. Crit Care Med, 1998, 26, 1536-1544.

ANGSTWURM, MW., SCHOTTDORF, J., SCHOPOHL, J. et al. Selenium replacement in patients with SIRS improves clinical aoutcome. Crit care Med, 1999, 27, p. 1807-1813.

MISHRA,V., BAINES,M., PERRY,SE., et al. Effect of selenium supplementation on biochemical markers and outcome in critically ill patients. Clin Nutrition, 2007, 26, p. 41-50.

ANGSTWURM, MW., ENGELMANN, L., ZIMMERMANN,T. Selenium in intensive care (SIC) study: results in patients with severe SIRS, sepsis and septic shock. Crit Care Med, 2007, 35, 1, p. 1-9.

BERGER, MM., CHIOLÉRO, RL. Antioxidant supplementation in sepsis and systemic inflammatory response syndromea. Crit Care med, 2007, 35, 9 Suppl, S.584-590.

KAZDA A.,Referát z Evropského sjezdu intenzivní medicíny Brusel 2009.

REINHART, K., MEISNER, M., BRUNKHORST, FM. Markers for sepsis diagnosis: what is useful? Crit Care Clin, 2006, 22, p. 503-519.

ROTHENBURGER, M., MARKEWITZ, A., LENZ, T., et al. Detection of acute phase response and infection. The role of procalcitonin and C-reactive protein. Clin Chem Lab Med, 1999, 37, p. 275-279.

BERNARD, L., FERRIERE, F., CASASSUS, P., et al. Procalcitonin as an early marker of bacterial infection in severely neutropenic febrile adults. Clin Infect Dis, 1998, 27, p. 914-915

DE BONT, ES., VELLENGA, E., SWAANENBURG, J., et al. Procalcitonin: a diagnostic marker of bacterial infection in neutropenic cancer patients with fever? Infection, 2000, 28, p. 398-400.

CHRIST-CRAIN, M., JACCARD-STOLZ, D., BINGISSER, R., et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet, 2004, 363, p. 600-607.

MARUNA, P. Prokalcitonin. Triton, Praha, 2003, 140 s.

RUOKONEN, E., NOUSIAINEN, T., PULKKI, K., et al. Procalcitonin concentrations in patients with neutropenic fever. Eur J Clin Microbiol Infect Dis, 1999, 18, p. 283-285.

SCHNEIDER, HG., LAM, QT. Procalcitonin for the clinical laboratory: a review. Pathology, 2007, 39, p. 383-390.

TANG, BM., ESLICK, GD., CRAIG, JC., et al. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis, 2007, 7, p. 210-217.

CASTELLI GP, POGNANI C, MEISNER M, et al. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. Crit Care 2004;8(4):R234-242.

GIAMARELLOU H, GIAMARELLOS-BOURBOULIS EJ, REPOUSSIS P, et al. Potential use of procalcitonin as a diagnostic criterion in febrile neutropenia: experience from a multicentre study. Clin Microbiol Infect 2004;10(7):628-633.

AMERICAN COLLEGE OF CHEST PHYSICIANS/SOCIETY OF CRITICAL CARE MEDICINE Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20(6):864-874.

SABAT R, HOFLICH C, DOCKE WD, et al. Massive elevation of procalcitonin plasma levels in the absence of infection in kidney transplant patients treated with pan-T-cell antibodies. Intensive Care Med 2001;27(6):987-991.

ZAZULA R, PRUCHA M, TYLL T, et al. Induction of procalcitonin in liver transplant patients treated with anti-thymocyte globulin. Crit Care 2007;11(6):R131.

DORNBUSCH HJ, STRENGER V, KERBL R, et al. Procalcitonin and C-reactive protein do not discriminate between febrile reaction to anti-T-lymphocyte antibodies and Gram-negative sepsis. Bone Marrow Transplant 2003;32(9):941-945.

DORNBUSCH HJ, STRENGER V, SOVINZ P, et al. Non-infectious causes of elevated procalcitonin and C-reactive protein serum levels in pediatric patients with hematologic and oncologic disorders. Support Care Cancer 2008;16(9):1035-1040.

Y. SAKR[1], K. REINHART, F. BLOOS, G. MARX, S. RUSSWURM, M. BAUER AND F. BRUNKHORST Time course and relationship between plasma selenium concentrations, systemic inflammatory response, sepsis, and multiorgan failure British Journal of Anaesthesia, doi:10.1093/bja/aem091, 2007

LORTON F, VEINBERG F, IELSCH D, et al. Procalcitonin serum levels in children undergoing chronic haemodialysis. Pediatr nephrol 2007;22(3):430-435.

STEINBACH G, BOLKE E, GRUNERT A, et al. Procalcitonin in patients with acute and chronic renal insufficiency. Wien Klin Wochenschr 2004;116(24):849-853.

ZIMA T., LABORATORNÍ DIAGNOSTIKA Galén, Karolínum 2007

STENVINKEL P, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int. 1999. 55(5):1899-911.

ALEXIEWICZ, J.M., ET AL., Impaired phagocytosis in dialysis patients: studies on mechanisms. Am J Nephrol, 1991. **11**(2): p. 102-11

HAAG-WEBER, M. AND W.H. HORL, Dysfunction of polymorphonuclear leukocytes in uremia. Semin Nephrol, 1996. **16**(3): p. 192-201.

STEINBACH G, BOLKE E, GRUNERT A, STORCK M, ORTH K. Procalcitonin in patients with acute and chronic renal insufficiency. Wien Klin Wochenschr 2004;116:849-853.

WARD RA, MCLEISH KR. Oxidant stress in hemodialysis patients: What are the determining factors? Artif Organs 2003; 27:230 –236.

BLUMBERG A, et al. Behaviour of beta 2-microglobulin in patients with chronic renal failure undergoing hemodialysis, hemodiafiltration and continuous ambulatory peritoneal dialysis (CAPD). Clin Nephrol. 1987. 27(5):245-9.

DUNTAS LH Selenium and inflammation : underlying anti inflammatory mechanisms. Horm Metab Res. 2009 Jun, 41(6): 443-447

ROSENTHAL S.H., MARGGHRAFT G.,HIRSCH T., JAKOB H.G., PHILIPP T., KRIBBEN A. Modulation and Source of Procalcitonin in Reduced Renal Function and

Renal Replacement Therapy. Scandinavian Journal of Immunology 61,p. 180-186. 2005

KALOCHERETIS P., REVELA J., SPANOU E., DROUZAS A., MAKRINIOUTOU I., IATROU CH. Strong Correlation of Beta2-microglobulin with Procalcitonin in the Serum of Chronic Hemodialysis Patients: A Role for Infections in the Dialysis- Related Amyloidosis. Renal Failure Vol. 30, No 3.,March 2008 pp.261-265

BRODSKA H., MALICKOVA K., UHROVA J., KAZDA A., BENAKOVA H., ZIMA T. Procalcitonin and Parameters of Bone Metabolism in Dialysed Patients Critical Care 2008, **12**(Suppl 2):P179 (13 March 2008)

BRODSKA H., KAZDA A., VALENTA J., HENDL J. Effect of High-dose Selenium Substitution on Selected Laboratory Parameters and Prognosis in Critically Ill Patients Critical Care 2009, **13**(Suppl 1):P150 (13 March 2009)

11. PUBLICATIONS OF THE AUTHOR

ORIGINAL PAPERS WITH IMPACT FACTOR

(RELATED)

1. Marked increase of procalcitonin after the administration of anti-thymocyte globulin in patients before haemopoietic stem cell transplantation does not indicate sepsis: a prospective study

Helena Brodska, Tomas Drabek, Karin Malickova, Antonin Kazda, Antonin Vitek, Tomas Zima, Marketa Markova

Critical Care 2009, **13**:R37 (16 March 2009), IF 4,55

2. Plasma calprotectin in chrinically dialysed end stage renal disease patients

Karin Malickova Helena Brodska, Jana Lachmanova, Sylvie Dusilova Sulkova, Ivana Janatkova, Helena Mareckova, Vladimir Tesar and Tomas Zima

Inflammation research 2009, odesláno IF 1,65

ORIGINAL PAPERS WITH IMPACT FACTOR
(not related)

3. Determination of pregnancy-associated plasma protein A in patients with vasculary disorders by time resolved amplifield craptate emission technology.

Zima T,Fialová L.,Malbohan I.,Soukupová J,Brodská H.,Mikulíková J.,Kunštář J.Žák A., Kraml .P .Clin Chem Lab Med 2002 40,spec.supl.309 IF 1,88

4. Soluble isoforms of CEACAM1 containing the A2 domain: increased serum levels in patients with obstructive jaundice and differences in 3-fucosyl-N-acetyl-lactosamine moiety
Draberova L., Cerna H., Brodska H., et al: **I**mmunology Volume: 101 Issue: 2 Pages**:** 279-287 Published: OCT 2000 IF 3,43

ORIGINAL PAPERS WITHOUT IMPACT FACTOR

1. Brodská H. Laboratorní monitoring In Idiopatické střevní záněty. M. Lukáš et al. Galén 1998

2. Brodská H. , Kotrlíková E. Laboratorní diagnostika malnutrice a biochemické monitorování při podávání umělé výživy. In Výživa pacientů s idiopatickými střevními záněty. P. Kohout a kol. Maxdorf 2004
3. Brodská H. Laboratorní diagnostika malnutrice In Základy klinické výživy Kohout P.,Kotrlíková E. , Krigl, Praha 2005
4. Broská H., Křemen J. Diagnostika malnutrice In Enterální a parenterální výživa M. Křemen Mladá Fronta 2009
5. Brodská H. Hospodaření s vodou a minerály, ledviny, moč InObecná a klinická biochemie pro bakalářské obory studia P. Štern, P. Kocna skripta na CD rom, Praha 2004
6. A. Kazda, H. Brodska, J.Valenta, M.Stříteský, J.Hendl, H.Benáková, J.Vondráček, M.Machová Kyslíkové parametry v kritických stavech.Klin.Biochem a metab.6(27)1998 No1, p 6-10
7. Kazda A.,Valenta J.,Brodská H.,Stach Z.,Hendl j.,Stříteský M PCT u kriticky nemocných Klin.biochemie a metabolismus 13 2005 č.1 str 4-9
8. Kazda A.,Brodská H.,Valenta J.,Uhrová J.,JHendl J., Bělohlávek J.,Stříteský M.:Prokalcitonin u akutních pankreatitid a v septických stavech...Klin.biochem a metab200210/1/32-37.
9. Valenta, J., Jabor, A, Brodská, H. Stach, Z., Kazda, A., Stříteský, M., Analýza diagnostické efektivity reaktantů akutní fáze u kriticky nemocných Anestézie a intenzivní medicína 17, 2006 č.3, s. 164-170
10. Kazda A.,Brodská H.,Valenta J.,Bláha j., Vinglerová M., Stříteský M., Čermák D., Urban.T., Zima T. Problematika sledování a suplementace zinku a selenu v intenzivní péči Klin.biochemie a metabolismus 12(33), 2004 p.184-189

Posters from international congreses, published in publications with impact factor.

1. Brodská H., Kazda A., Bláha J., Vinglerová M.,Čermák D.,Valenta J., Zima T. Monitoring of selenium and zinc plasmatic levels et intensive care patients Euromedlab 2003,Monduzzi editores pA. Medimont.inc. Bologna Italy page 253-256

2. Kazda A.,Brodská H.,Valenta J.,Uhrová J.,Hendl J.,Bělohlávek J.,Stříteský M.: Procalcitonin in critically ill patients EUROMEDLAB 2001 poster

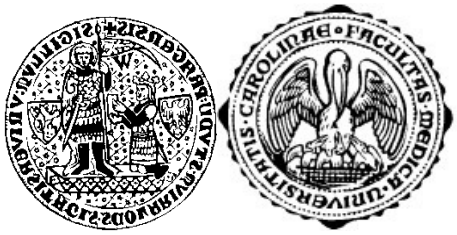
3. Kazda A., Valenta J., Brodska H., Stříteský M., Stach Z.,Hendl J. PCT in critical ill. Poster 25th International symp. of Intensive care and Emergency med. Brusel 21.-25.4.2005, sb.Critical Care 2005 supl.1 str.273

4. Kazda A., Brodska H., Valenta j., Vinglerová M., Hendl j., Stach Z., Slabá I., Nosková P., Otčenášek m., Součková A. Selen and its substitution in critically ill. Critical Care vol.10 supplement 1 March 2006
5. Valenta J., Jabor A., Brodska H., Stach Z., Kazda A., Stříteský M. Procalcitonin: analysis of diagnostic specificity and effectivity in comparison with other markers of inflammation in the critically ill. Critical care Vol.10, supplement 1, March 2006
6. Valenta J, Jabor A, Brodska H, Stach Z, Kazda A, Stritesky M. Procalcitonin: analysis of diagnostic specificity and effectivity in comparison with other markers of inflammation in the critically ill. Critical Care 2006, **10**(Suppl 1):P74 (21 March 2006)

7. Brodska H.,Kazda A.,ValentaJ. High dose of selenium in critically ill....ESPEN kongres 2007 Praha přednáška, otištěno Clinical nutrition suppl.2, p.20-21
8. Brodska H, Malickova K,Kazda A,Lachmanova J,Uhrova J, Zima T. The elevation of Procalcitonin in chronicaly dialysed patients, Critically care 2008, 12 suppl.2: P 179...
9. H.Brodska , A.Kazda , J.Valenta , J.Hendl :Effect of high dose selenium substitution on selected laboratory parametres and prognosis in critically ill patients. Poster Brusel 2009, Critacally care 2009, Volume 13, suppl.1, page62.
10. Karin Malickova1, Helena Brodska1, Jana Lachmanova2, Sylvie Dusilova Sulkova 1,3, Ivana Janatkova1, Helena Mareckova1, 4, Vladimir Tesar2 and Tomas Zima1 :Plasma Calprotectin in Chronically Dialyzed End-Stage Renal Disease Patients Poster Euromedlab 2009
11. Kazda A, Brodska H, Vinglerova H, Blaha J, Valenta J, Stritesky M, Zima T, Urban M., Selenium and Zinc placatic levels in intensit care patiens. Critical Care 2004, **8**(Suppl 1):P265 (15 March 2004)

ABSTRACTS AND ORIGINAL PAPER WITHOUT IMPACT FACTOR

1. Brodská H., Kazda A.,Bláha J., Vinglerová M., Čermák D., Valenta J., Zima T. Sledování plasmatických hladin Se a Zn u pacientů v intenzivní péči, celostátní sjezd ČSKB Hradec Králové 9/03, publikace ve sborníku ISBN 80-2391885-0
2. Brodska H.:Biochemické monitorování kriticky nemocných, dg.malnutrice přednáška,sborník 10.pražské chirurgické dny 2001
3. Kazda A., Brodská H., Bláha J.,Vinglerová M., Čermák D., Valenta J., Zima T. Sledování hladin Se a Zn o pacientů v intenzivní péči. Sborník ze sjezdu Slovenské společnosti pro parenterální a enterální výživu, Bánská Bystrica 11/03
4. Brodská H., Kazda A., Prokalcitonin a PAF u kriticky nemocných přednáška Nejedlého den, Kladno 21.4.2005
5. Kazda A., Brodská H., Valenta J., Stach Z., Hendl J., Stříteský M., Jabor A. PCT, CRP a další reaktanty akutní fáze v intenzivní péči, Sjezd SKVIMP Hradec Králové 3.-5.3.2005 sborník 48-49 ISBN 80-86225-69-0
6. Kazda A., Brodská H., Valenta J., Vinglerová M., Hendl J., Stach Z., Slabá I., Nosková P., Otčenášek M., Součková A. Selen a jeho substituce u kriticky nemocných Sjezd Spol.klinické biochemie Olomouc 11.-13.9.2005 Sborník 41 ISBN 80-2139-5267-6
7. Kazda A., Valenta J., Brodská H., Stach Z., Hendl J.,Stříteský M. PCT v kritických astavech Sjezd ARIM Olomouc 8.-10.9.2005 Sborník str.153 ISBN 80-72-62-353-2
8. Valenta J., Jabor A., Brodská H., Stach Z., Kazda A., Stříteský M. Analýza diagnostické efektivity reaktantů akutní fáze v kritických stavech. 7.kardioanesteziologické dny s mezinárodní účastí, Pardubice 28.-30.4.2005, sborník 20 ISBN 80-86857-02-06
9. Brodská H, Kazda A., Valenta J., Vinglerová M., Hendl J.,Pelinkova K; Stach Z., Slabá I., Nosková P., Otčenášek M., Součková. Selen a jeho substituce u kriticky nemocných FONS 2006 přednáška, sborník
10. Zima T, Brodská H.,Kazda A. Laboratorní metody na počátku 3. tisíciletí a jejich přínos v péči o kriticky nemocné Celostátní sjezd ARIM, Kroměříž 2006, abstrakta ve sborníku



Charles University in Prague

1st Faculty of Medicine

MONITORING OF BIOCHEMICAL MARKERS OF SEPTIC STATES.

(PhD Thesis Summary)

MUDr Helena Brodská

Prague 2009